# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>19025.023 | **FOR FURTHER ACTION** | See item 4 below |
| International application No.<br>PCT/US2004/026309 | International filing date *(day/month/year)*<br>16 August 2004 (16.08.2004) | Priority date *(day/month/year)*<br>21 July 2004 (21.07.2004) |
| International Patent Classification (8th edition unless older edition indicated)<br>See relevant information in Form PCT/ISA/237 | | |
| Applicant<br>PTC THERAPEUTICS, INC. | | |

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☒ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

| | |
|---|---|
| | Date of issuance of this report<br>23 January 2007 (23.01.2007) |
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland<br><br>Facsimile No. +41 22 338 82 70 | Authorized officer<br><br>Athina Nickitas-Etienne<br><br>e-mail: pt04@wipo.int |

# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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WASHINGTON, DC 20004

PCT



## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Applicant's or agent's file reference<br>19025.023 | Date of mailing (*day/month/year*) 13 JUL 2005<br>**FOR FURTHER ACTION**<br>See paragraph 2 below |

| International application No. | International filing date (*day/month/year*) | Priority date (*day/month/year*) |
|---|---|---|
| PCT/US04/26309 | 16 August 2004 (16.08.2004) | 21 July 2004 (21.07.2004) |

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C12Q 1/70; C12Q 1/68; C12N 15/63 and US Cl.: 435/6, 320.1

Applicant

PTC THERAPEUTICS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☒ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/ US | Authorized officer |
|---|---|
| Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450 | Daniel M. Sullivan *J. Roberts for* |
| Facsimile No. (703) 305-3230 | Telephone No. (571) 272-1600 |

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US04/26309

**Box No. I Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/26309

**Box No. IV Lack of unity of invention**

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:
   - ☒ paid additional fees
   - ☐ paid additional fees under protest
   - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-24, 31-35 and 37-54

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US04/26309

**Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Claims 1-24, 31-35, 37-54 | YES |
| | Claims NONE | NO |
| Inventive step (IS) | Claims 31-35, 37-40, 42, 50-54 | YES |
| | Claims 1-24, 41, 43-49 | NO |
| Industrial applicability (IA) | Claims 1-24, 31-35, 37-54 | YES |
| | Claims NONE | NO |

2. Citations and explanations:

Claims 41 and 43-49 lack an inventive step under PCT Article 33(3) as being obvious over US 6,448,007.

The claims are directed to a method of screening for a compound that modulates protein expression through an UTR-affected mechanism comprising growing a stable cell line having a reporter gene proximally linked to the target UTR, comparing the stable cell line in the presence of a compound relative to an absence of said compound and selecting for said compound that modulates protein expression through an UTR-affected mechanism. The teachings of the '007 patent are primarily directed to methods of identifying regulatory UTRs by creating libraries wherein reporter genes are fused to various cellular UTRs and expressed in cells. The methods described therein comprise sorting cells on the basis of relative levels of reporter gene expression (see especially the Summary of the Invention section). In the third paragraph in column 8, the '007 patent teaches, "[a] similar strategy can be used to screen and identify compounds that affect the function of the 5' and 3' UTR regulatory elements. Compounds that modulate the UTR effect on gene expression would skew the expression of the UTR-linked gene as compared to gene expression in the absence of the compound. In view of these teachings, the method of claims 41 and 43 would be obvious the skilled artisan. Furthermore, claims 44-49, which depend from claim 43, merely limit the UTR or cell used in the assay to having certain properties that would be inherent to many UTRs and cells and do not represent an inventive step over the teachings of the '007 patent.

Claims 1-24 lack an inventive step under PCT Article 33(3) as being obvious over US 6,448,007 in view of Ismail et al. (2000) J. Virol. 74:2365-2371 and further in view of US 5,859,227.

As described above, the '007 patent teaches processes which involve using vector constructs comprising reporter genes operably linked to UTR regulatory sequences. The '007 patent does not teach that the vectors used therein comprise an intron or an IRE according to the elected invention. However, the '007 patent does teach that a retroviral vector can be used to deliver the nucleic acids used in the assays described therein (see especially the paragraph bridging columns 6-7). Ismail *et al.* teaches enhancement of transgene expression by inclusion of an intron in a retroviral vector (see throughout). Thus, it was recognized in the art that it is desirable to include introns when expressing genes from retroviral vectors. Therefore, this limitation does not represent an inventive step over the art. Furthermore, the '227 patent teaches that the elected iron response element was known in the art and recognized as an important UTR element worthy of study in an assay of UTR regulation (see especially column 25, paragraph 3). Thus, the elected invention as a whole would be obvious in view of the available art. The dependent claims merely recite parameters such as the position of the intron, the linkage of the UTR and the reporter, properties of the vector that are conventional in the art and do not represent an inventive step.

Claims 31-35, 37-40 ,42 and 50-54 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the methods claimed. In particular, the art fails to teach or provide motivation to practice the method of claims 31-35 and 37-40 wherein the nucleic acid comprises both a 5' and 3' UTR flanking the reporter gene, or the method of claims 50-54 wherein the reporter gene is proximally linked to more than one target UTR.

Claims 1-24, 31-35 and 37-54 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/26309

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 41-54 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims are indefinite for the following reason(s): The claimed methods recite that the stable cell lines are compared in the presence and absence of the compound but do not indicate what aspects of the cell lines are compared. It is assumed that expression of the reporter gene is the measured parameter.